ORIGINAL RESEARCH

# Relations of Sex to Diagnosis and Outcomes in Acute Coronary Syndrome

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***Background*—**The atypical presentation of women with acute coronary syndrome (ACS) has been related to delayed diagnosis and treatment, which may explain worse outcome compared with men.

***Methods and Results*—**We analyzed pooled data of 2520 patients of 2 prospective cohorts in terms of differences in presentation and management of women and men suggestive of ACS. Using logistic regression, we established 2 diagnostic models and tested their diagnostic performance in both sexes separately. Sex-specific differences in management of patients with ACS were ascertained and a 2-year follow-up was performed. Women were older than men (median 67 versus 61 years, $P$=0.001), had more often dyspnea (22% versus 18%, $P$=0.024), nausea or vomiting (26% versus 16%, $P$=0.001) and radiating chest pain (47% versus 40%, $P$=0.001). Classical risk factors (smoking, diabetes mellitus, dyslipidemia or known coronary artery disease) were less frequent in women. Diagnostic models showed no significant sex-related differences in diagnostic performance in a "first contact" setting (medical history and symptoms) or after "complete triage" (including ECG and biomarkers). Women with ACS underwent coronary angiography (73.8% versus 84.3%, $P$<0.001) and revascularization (53.8% versus 70.1%, $P$<0.001) less frequently. Two-year incidence of myocardial infarction and death was similar in both sexes, but revascularization and cardiac rehospitalization were more frequent in men.

***Conclusions*—**In a large cohort of patients with suspected ACS, sex differences in clinical presentation did not impair diagnostic accuracy. Two-year outcomes were comparable. Our findings suggest a benefit of chest pain units to minimize sex differences in ACS management and prognosis.

***Clinical Trial Registration*—**URL: https://www.clinicaltrials.gov. Unique identifiers: NCT02355457 (BACC), NCT03227159 (stenoCardia). **(*J Am Heart Assoc*. 2018;7:e007297. DOI: 10.1161/JAHA.117.007297.)**

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There is evidence for sex-specific differences in patients presenting to emergency departments with suspected acute coronary syndrome (ACS).[1–3] There is an ongoing debate whether a presentation with "atypical" symptoms, eg, not severe chest discomfort, only for a short time, missing of chest pain at all or dyspnea, nausea and vomiting is more common among women and if it affects diagnosis and treatment.[4–6]

Actual guidelines for management of patients suggestive of ACS recommend an immediate assessment of symptoms, medical history, cardiovascular risk factors, physical examination, ECG, and blood biomarkers.[7,8] These

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Accompanying Data S1, Tables S1 through S8, and Figure S1 through S4 are available at http://jaha.ahajournals.org/content/7/6/e007297/DC1/embed/inline-supplementary-material-1.pdf

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## Clinical Perspective

### What Is New?

- In a large contemporary cohort of patients with suspected myocardial infarction, differences in presentation and management of women and men were observed, but intermediate term outcome was comparable.
- Diagnostic models developed with the help of different variable selection methods showed comparable diagnostic accuracy in both sexes.

### What Are the Clinical Implications?

- Sex-related differences in patients with acute coronary syndrome may be addressed by standardized diagnostic algorithms as implemented in chest pain units.
- Such strategies may reduce sex differences in outcomes.

recommendations are built on data of half a century of cardiovascular research. Coronary artery disease is more common in men.[9] Patients presenting with suspected ACS to the emergency department are almost twice as likely to be men[10–12] and women are underrepresented in these studies. In addition, while cardiovascular mortality is declining in Western countries because of improved diagnostics and therapies, women do not profit to the same extend.[13] Furthermore, women with need for percutaneous coronary intervention showed a higher mortality risk than men.[14] A recent study suggested that the diagnostic accuracy of ACS is similar in women and men.[15] However, data have remained inconsistent and evidence from patients managed in modern chest pain units (CPU) remains scarce. In particular, the relevance of potential sex differences in outcome are not well understood.

We therefore analyzed data of 2 prospective studies of patients with signs and symptoms suggestive of ACS for sex differences in clinical presentation to the emergency department. We further developed diagnostic models to predict ACS at "first contact" (clinical variables, symptoms, risk factors, medical history) and after "complete triage" (including ECG information and biomarker results) and analyzed their diagnostic performance in both sexes. Finally, we compared outcome data on major adverse cardiovascular events and mortality in women and men.

## Methods

### Data Availability

The data, analytic methods, and study materials will be made available to other researchers on demand for purposes of reproducing the results or replicating the procedure. Respective requests should be submitted to the corresponding author.

### Biomarkers in Acute Cardiac Care Study Population

The BACC (Biomarkers in Acute Cardiac Care) study has been described previously.[10] Briefly, we included 1625 patients presenting to the emergency department of the University Heart Center Hamburg with suspected ACS. All patients were enrolled between July 2013 and March 2016. The inclusion criteria were suspected ACS, age > 18 years, and the ability to provide written informed consent.

The BACC study was registered at https://www.clinicaltrials.gov (unique identifier: NCT02355457).

### StenoCardia Study Population

The stenoCardia study included 1818 patients with acute chest pain presenting to 3 German emergency departments (Mainz, Koblenz, Hamburg) between 2007 and 2008. The methodology, follow-up, and adjudication of outcomes have been reported in detail previously.[16] The stenoCardia study was registered at https://www.clinicaltrials.gov (unique identifier: NCT03227159).

Both cohorts comply with the Declaration of Helsinki and were approved by the local Ethics Committees.

### The Standard Diagnostic Approach and Adjudication of the Final Diagnosis

In both studies, a routine ECG was collected on admission by trained medical staff. ECG results were interpreted by the emergency physician and re-evaluated by a cardiologist. The diagnosis was based on all available clinical and imaging results, ECG, standard laboratory testing, including in-house cardiac troponins: In BACC, the Elecsys Roche high-sensitivity troponin T (Roche Diagnostics, Germany) was used for adjudication, in stenoCardia 2 sensitive troponin assays were used for adjudication: fourth generation Elecsys troponin T assay, (Roche Diagnostics, Germany used in Mainz and Hamburg) and the Architect STAT troponin I system (Abbott Diagnostics, Abbott Park, IL used in Koblenz).[16]

The final diagnosis of all patients in both studies was made independently by 2 cardiologists. In cases of disagreement, a third cardiologist's review was obtained.

Because of methodological differences, some symptom variables were not available in both studies.

### Patient Management and Follow-Up

Treatment during the index event was assessed including coronary angiography and revascularization therapy

(percutaneous coronary intervention or coronary artery bypass grafting). To understand the degree of stenosis in patients with coronary artery disease we calculated the SYNTAX Score.[17] We used the SYNTAX Score I online tool (http://www.syntaxscore.com/calculator/syntaxscore/frameset.htm, last accessed September, 21 2017). In the BACC study SYNTAX Score was only available for the first 1000 included patients.

In both studies, follow-up was performed via telephone, questionnaires mailed to the participants, general practitioner and/or electronic medical records. The local registry offices were contacted to ascertain mortality and acquire death certificates. The median follow-up time in the BACC-study was 438 days, in stenoCardia 1204 days.

## Study Specific Measurements

For study purposes, troponin I was measured using a high-sensitivity troponin I (hs-TnI) immunoassay (Abbott Diagnostics, ARCHITECT i1000SR). The test specific limit of detection was 1.9 ng/L (range 0–50 000 ng/L), with a 10% coefficient of variation at a concentration of 5.2 ng/L. The intra-assay and inter-assay coefficients of variation of this assay were 4.26% and 6.29%.[18] The 99th percentile has been described at 27 ng/L in the general population.[19]

## Statistical Analyses

### *Pooling of BACC and stenoCardia data sets*

Individuals from the BACC cohort (N=1625) the stenoCardia cohort (N=1818) were screened. There were 923 individuals excluded because of missing values among the variables of interest, leaving 2520 patients for analyses. To understand possible selection bias, we provide clinical characteristics of patients excluded from analyses in Table S1.

### *Baseline characteristics*

For continuous variables quartiles are given, for binary ones frequencies. For comparison of women and men the Fisher exact test was used for binary variables and the Mann–Whitney test for continuous ones, respectively. ECG variables are referring to the ECG conducted on admission. Estimated glomerular filtration rate was computed following the Chronic Kidney Disease Epidemiology Collaboration (CKD EPI) formula.[20]

### *Logistic regressions*

To examine the association of the candidate predictors with the final ACS diagnosis, logistic regressions were performed. Besides the independent variables, the models included sex, a study indicator (BACC, stenoCardia) and an interaction term between the candidate predictor and sex as covariates. Sex specific confidence intervals (and *P*-values) for the predictors' odds ratios were computed using the methods described in Figueiras et al.[21]

### *Generation of diagnostic models for ACS and comparison of their diagnostic performance in both sexes*

With the help of least absolute shrinkage and selection operator (LASSO),[22] regression models for prediction of ACS were generated: The first model included only variables available directly on "first contact" (clinical variables, symptoms, risk factors, medical history), the second model included variables available after "complete triage" of patients (addition of ECG information and biomarker results). A cohort variable was forced into the models to adjust for differences of the 2 cohorts. The LASSO penalization parameter lambda was chosen by optimization of the mean deviance in 10-fold cross-validation. The chosen penalization parameter was the largest lambda within one standard error of the minimum. Receiver operating characteristics (ROC) curves and area under the curve (AUC) estimates were corrected for over-optimism using bootstrapping with 500 iterations. An analysis flowchart illustrating the pooling of both cohorts and performance of the LASSO analysis is provided in Figure S1). A detailed description of the LASSO method is provided in Data S1.

To compare the LASSO generated models with an alternative variable selection procedure, variable importance according to random forest were computed. Random forest was applied to "first-contact" variables and variables after "complete triage." Each forest consisted of 1000 classification trees. The permutation variable importance measure of random forest was computed for each group of variables. Each tree was grown on a bootstrap sample of the original data set (this bootstrap sample has the same number of individuals as the original sample, but an individual may be sampled more than once).[23]

### *Outcome analyses*

Survival curves for mortality, myocardial infarction, revascularization therapy and cardiac rehospitalization were generated using the Kaplan–Meier method. For comparison of survival curves between women and men the log-rank test was applied.

All analyses were performed using R software, version 3.3.3 (R Development Core Team, 2017; R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. ISBN 3-900051-07-0, URL https://www.R-project.org).

**Table 1.** Baseline Characteristics

| | Women (N=880) | Men (N=1640) | *P* Value |
|---|---|---|---|
| Age, y | 67 (55, 75) | 61 (50, 71) | <0.001 |
| Cardiovascular risk factors | | | |
| Body mass index, kg/m$^2$ | 25.8 (23.0, 29.7) | 27.0 (24.8, 30.1) | <0.001 |
| Systolic blood pressure, mm Hg | 145 (130, 161) | 143 (129, 158) | 0.039 |
| Heart rate, bpm | 74 (65, 84) | 74 (64, 85) | 0.92 |
| Current smoker, % | 168 (19.1) | 438 (26.7) | <0.001 |
| Diabetes mellitus, % | 106 (12.0) | 235 (14.3) | 0.11 |
| Dyslipidemia, % | 493 (56.0) | 992 (60.5) | 0.030 |
| History of coronary artery disease/bypass/PCI, % | 224 (25.5) | 605 (36.9) | <0.001 |
| Family history of coronary artery disease, % | 233 (26.5) | 434 (26.5) | 1.00 |
| Congestive heart failure, % | 62 (7.0) | 147 (9.0) | 0.11 |
| Atrial fibrillation, % | 119 (13.5) | 186 (11.3) | 0.11 |
| Stroke, % | 52 (5.9) | 89 (5.4) | 0.65 |
| Symptoms | | | |
| Chest pain, % | 781 (88.8) | 1492 (91.0) | 0.079 |
| Radiating chest pain, % | 410 (46.6) | 650 (39.6) | <0.001 |
| Dyspnea (NYHA III or IV), % | 195 (22.2) | 301 (18.4) | 0.024 |
| Nausea or vomiting, % | 228 (25.9) | 255 (15.5) | <0.001 |
| Diaphoresis, % | 136 (15.5) | 293 (17.9) | 0.13 |
| ≤1 Symptom, % | 143 (55.0) | 364 (56.2) | 0.77 |
| 2 to 3 Symptoms, % | 113 (43.5) | 278 (42.9) | 0.88 |
| >3 Symptoms, % | 4 (1.5) | 6 (0.9) | 0.48 |
| Symptom onset time <3 h, % | 285 (33.4) | 565 (35.5) | 0.31 |
| 3 h ≥ Symptom onset time ≤6 h, % | 150 (17.6) | 255 (16.0) | 0.33 |
| Symptom onset time >6 h, % | 418 (49.0) | 770 (48.4) | 0.80 |
| ECG findings | | | |
| ST-segment elevation, % | 126 (14.3) | 424 (25.9) | <0.001 |
| ST-segment depression, % | 101 (11.5) | 226 (13.8) | 0.11 |
| T-wave inversion, % | 183 (20.8) | 364 (22.2) | 0.45 |
| Left or right bundle branch block, % | 66 (7.5) | 173 (10.5) | 0.013 |
| Biomarkers | | | |
| Hs-TnI on admission, ng/L | 6.1 (2.7, 21.8) | 8.3 (3.8, 35.3) | <0.001 |
| eGFR, mL/min for 1.73 m$^2$ | 75 (59, 92) | 84 (69, 96) | <0.001 |
| Final diagnosis | | | |
| All acute coronary syndrome, % | 260 (29.5) | 648 (39.5) | <0.001 |
| ST-elevation myocardial infarction, % | 33 (3.8) | 110 (6.7) | 0.0021 |
| Non-ST-elevation myocardial infarction, % | 135 (15.3) | 308 (18.8) | 0.032 |
| Unstable angina pectoris, % | 92 (10.5) | 230 (14.0) | 0.010 |

Baseline characteristics are given for women and men. The *P*-values are for Fisher's exact test for categorical variables or the Mann–Whitney test for continuous ones. For continuous variables the quartiles are given, for binary ones frequencies. The quartiles are given on the following format: Median (25th percentile, 75th percentile). eGFR indicates estimated glomerular filtration rate; hs-TnI, high-sensitivity troponin I; NYHA, New York Heart Association; PCI, percutaneous coronary intervention.

**Table 2.** Logistic Regression Models for Prediction of ACS Including Interaction With Sex

| Predictor of Interest | Sex Interaction *P* Value | Category | OR (95% CI) | *P* Value |
|---|---|---|---|---|
| Age | 0.63 | Women | 1.03 (1.02, 1.04) | <0.001 |
| | | Men | 1.03 (1.03, 1.04) | <0.001 |
| Body mass index | 0.045 | Women | 0.98 (0.96, 1.01) | 0.25 |
| | | Men | 1.02 (1.00, 1.04) | 0.082 |
| Systolic blood pressure | 0.0064 | Women | 1.00 (0.99, 1.00) | 0.23 |
| | | Men | 1.01 (1.00, 1.01) | 0.0028 |
| Heart rate (log) | 0.38 | Women | 1.50 (0.76, 2.93) | 0.24 |
| | | Men | 1.05 (0.66, 1.65) | 0.84 |
| Current smoker | 0.84 | Women | 1.21 (0.84, 1.72) | 0.31 |
| | | Men | 1.26 (1.01, 1.57) | 0.041 |
| Diabetes mellitus | 0.39 | Women | 1.53 (1.00, 2.32) | 0.049 |
| | | Men | 1.91 (1.45, 2.53) | <0.001 |
| Dyslipidemia | 0.22 | Women | 1.85 (1.37, 2.53) | <0.001 |
| | | Men | 2.34 (1.88, 2.92) | <0.001 |
| History of coronary artery disease/bypass/PCI | 0.0093 | Women | 3.17 (2.30, 4.36) | <0.001 |
| | | Men | 1.92 (1.56, 2.35) | <0.001 |
| Family history of coronary artery disease | 0.16 | Women | 0.84 (0.60, 1.17) | 0.31 |
| | | Men | 1.12 (0.90, 1.41) | 0.31 |
| Congestive heart failure | 0.60 | Women | 1.52 (0.88, 2.59) | 0.12 |
| | | Men | 1.28 (0.91, 1.81) | 0.16 |
| Atrial fibrillation | 0.072 | Women | 0.92 (0.59, 1.40) | 0.70 |
| | | Men | 0.56 (0.39, 0.78) | <0.001 |
| Stroke | 0.89 | Women | 1.05 (0.56, 1.90) | 0.87 |
| | | Men | 1.03 (0.66, 1.59) | 0.88 |
| Dyspnea (NYHA III or IV) | 0.69 | Women | 1.37 (0.97, 1.92) | 0.069 |
| | | Men | 1.49 (1.16, 1.92) | 0.0018 |
| Chest pain | 0.062 | Women | 0.92 (0.59, 1.47) | 0.73 |
| | | Men | 1.61 (1.11, 2.35) | 0.013 |
| Radiating chest pain | 0.77 | Women | 1.68 (1.25, 2.27) | <0.001 |
| | | Men | 1.60 (1.30, 1.97) | <0.001 |
| Nausea and vomiting | 0.93 | Women | 1.05 (0.75, 1.46) | 0.77 |
| | | Men | 1.03 (0.78, 1.36) | 0.82 |
| Diaphoresis | 0.41 | Women | 1.41 (0.95, 2.08) | 0.087 |
| | | Men | 1.71 (1.32, 2.22) | <0.001 |
| ST-segment depression | 0.96 | Women | 3.24 (2.13, 4.96) | <0.001 |
| | | Men | 3.29 (2.45, 4.43) | <0.001 |
| ST-segment elevation | 0.031 | Women | 3.16 (2.13, 4.69) | <0.001 |
| | | Men | 1.93 (1.52, 2.46) | <0.001 |
| T-wave-inversion | 0.13 | Women | 2.55 (1.81, 3.58) | <0.001 |
| | | Men | 1.86 (1.46, 2.36) | <0.001 |

Continued

**Table 2.** Continued

| Predictor of Interest | Sex Interaction *P* Value | Category | OR (95% CI) | *P* Value |
|---|---|---|---|---|
| Left or right bundle branch block | 0.46 | Women | 1.41 (0.82, 2.36) | 0.20 |
| | | Men | 1.11 (0.81, 1.53) | 0.51 |
| Log(hs-TnI) | 0.76 | Women | 2.29 (2.04, 2.60) | <0.001 |
| | | Men | 2.24 (2.05, 2.46) | <0.001 |
| eGFR | 0.062 | Women | 0.98 (0.97, 0.99) | <0.001 |
| | | Men | 0.99 (0.98, 0.99) | <0.001 |

Logistic regression models for ACS status include the predictor of interest x sex interaction. The models are adjusted for study cohort (BACC, stenoCardia). For each independent variable, a separate model was computed. CI indicates confidence interval; eGFR, estimated glomerular filtration rate; hs-TnI, high-sensitivity troponin I; NYHA, New York Heart Association; PCI, percutaneous coronary intervention.

# Results

## Baseline Characteristics

Women were older than men (median 67 versus 61 years, *P*=0.001). Classical risk factors like smoking (19.1% versus 26.7%, *P*<0.001), dyslipidemia (56.6% versus 60.5%, *P*=0.03), or a history of coronary artery disease (25.5% versus 36.9%, *P*<0.001) were less frequent in women. Some sort of chest pain was reported with a similar proportion in both sexes (88.8% versus 91.0%, *P*=0.079), while women more often presented with typical radiating chest pain (46.6% versus 39.6%, *P*<0.001), dyspnea (22.2% versus 18.4%, *P*=0.02) and nausea or vomiting (25.9% versus 15.5%, *P*<0.001). Time from onset of symptoms to presentation at the emergency department did not differ significantly in both sexes. Women showed worse kidney function (estimated glomerular filtration rate: 75 mL/min versus 84 mL/min, *P*<0.001) compared with men. In the initial ECG ST-segment elevation (14.3% versus 25.9%, *P*<0.001) and left or right bundle branch block (7.5% versus 10.5%, *P*=0.013) was more prevalent in men. Hs-TnI was lower in women (6.1 versus 8.3, *P*<0.001). Final diagnosis of ACS was less frequent in women (29.5% versus 39.5%, *P*<0.001) Female patients reported 2 or more symptoms at the same time more often than men (43.2% versus 37.3%, *P*=0.004) (Table 1).

Characteristics were similar when we restricted analyses to patients with a final diagnosis of ACS (Table S2). Baseline characteristics for the individual studies are available in Tables S3 and S4.

## Logistic Regression Analyses

Using logistic regression, the variables age, diabetes mellitus, dyslipidemia, history of coronary artery disease, radiating chest pain, ST-segment depression, inversion of T-wave, logarithmically transformed hs-TnI and, eGFR were associated with the final diagnosis of ACS in both sexes (Table 2). An interaction with sex indicating different strengths of association in women and men with the final diagnosis of ACS was observed for history of coronary artery disease with a higher odds ratio (OR) for women (OR 3.17 [confidence interval {CI} 2.30–4.36] for women and 1.92 [CI 1.56–2.35] for men) and ST-segment elevation on the first ECG (OR 3.16 [CI 2.13–4.69] for women and 1.93 [CI 1.52–2.46] for men). Systolic blood pressure also showed a significant interaction with sex and ACS (OR 1.00 [CI 0.99–1.00] for women and 1.01 [1.00–1.01]) for men.

To understand cohort specific associations of each variable with the diagnosis of ACS by sex we performed logistic regression analyses in both cohorts individually, showing mostly similar odds ratios in both cohorts (Tables S5 and S6).

## Development of Diagnostic Models

The variables chosen by LASSO regression and their respective ORs are given in Table 3. For comparison, an importance selection using random forests was performed. In the “first contact” model age and a history of coronary artery disease ranked highest in the random forest. Those and most of the other top variables were chosen by the LASSO as well. For the “complete triage” model ranking of variables was also comparable to the selection by LASSO (Figures S2 and S3).

Similar selection of variables and comparable odds ratios were observed when LASSO regression was performed in each cohort separately (Tables S7 and S8) Hs-TnI and heart rate were log-transformed..

## Comparison of Diagnostic Accuracy in Women and Men

Application of the LASSO derived diagnostic models to both sexes individually revealed nearly identical diagnostic performance for the “first contact” model (AUC 0.68 in women versus 0.69 in men, *P*=0.86). The addition of variables

**Table 3.** Odds Ratios for Variables Selected by LASSO Regression for the Diagnosis of ACS

| | "First Contact" | "Complete Triage" |
|---|---|---|
| | Odds Ratio | Odds Ratio |
| Age | 1.03 | 1.01 |
| Cardiovascular risk factors | | |
| Body mass index | | |
| Systolic blood pressure | | |
| Heart rate | | |
| Current smoker | 1.37 | 1.11 |
| Diabetes mellitus | 1.09 | 1.08 |
| Dyslipidemia | 1.32 | 1.33 |
| History of coronary artery disease/ bypass/PCI | 1.41 | 1.90 |
| Family history of coronary artery disease | | |
| Congestive heart failure | | 0.83 |
| Atrial fibrillation | 0.73 | 0.62 |
| Stroke | | |
| Symptoms | | |
| Chest pain | | 1.13 |
| Radiating chest pain | 1.36 | 1.26 |
| Dyspnea (NYHA III or IV) | 1.02 | |
| Nausea or vomiting | | |
| Diaphoresis | | |
| ECG findings | | |
| ST-segment depression | Not included | 1.35 |
| ST-segment elevation | Not included | 1.18 |
| T-wave-inversion | Not included | |
| Left or right bundle branch block | Not included | 0.86 |
| Biomarkers | | |
| Hs-TnI 0 h | Not included | 2.01 |
| eGFR | Not included | |

The LASSO penalization parameter lambda was chosen by optimization of the mean deviance in 10-fold cross-validation. Shown are the results for the parameter 1 standard error of the minimum. A study indicator was not allowed to be dropped from the model (Inclusion in the BACC-cohort OR 1.32 for "first contact" and 2.02 for "complete triage"). Hs-TnI and heart rate were log-transformed. eGFR indicates estimated glomerular filtration rate; hs-TnI, high-sensitivity troponin I; LASSO, least absolute shrinkage and selection operator; NYHA, New York Heart Association; PCI, percutaneous coronary intervention.

available after "complete triage" improved diagnostic performance in both sexes (AUC 0.88 in women versus 0.85 men, $P$=0.13). Diagnostic performance of hs-TnI alone reached comparable results (AUC 0.85 in women versus 0.82 in men, $P$=0.13) to the combined model after "complete triage" (Figure 1).

## Differences in Management of Women and Men

We observed significant differences in the management of women and men suggestive of ACS. Men were more likely to undergo coronary angiography (41.8% versus 33.4%, $P$<0.001) and coronary intervention (27.8% versus 16.1%, $P$<0.001). Women with a final diagnosis of ACS underwent coronary angiography (73.8% versus 84.3%, $P$<0.001) or coronary intervention (70.1% versus 53.8%, $P$<0.001) significantly less frequently than men. Analyses of the SYNTAX Score revealed less stenotic coronary artery disease in women compared with men (4.0 versus 9.0, $P$=0.001) in the overall cohort and in patients with ACS (9.0 versus 12.5, $P$=0.001) (Table 4).

## Comparison of Follow-Up Events of Women and Men

The overall study follow-up after 2 years showed no significant difference between women and men for overall death (4.97% versus 5.73%, $P$=0.42) or myocardial infarction (1.95% versus 2.37%, $P$=0.53). Revascularization was more often necessary in men (3.01% versus 7.58%, $P$<0.001). Rehospitalization for cardiac disease occurred more frequently in men (17.6% versus 21.1%, $P$=0.04) (Figure 2). In patients with a final diagnosis of ACS, a significant difference was observed for revascularization therapy (8.84% for women versus 14.41% for men, $P$=0.03) (Figure S4).

## Discussion

The key findings of our study are considerable differences between women and men admitted for suspected ACS in symptoms and clinical presentation. However, these did not translate into different diagnostic accuracy nor outcomes, ie, myocardial infarction or death rates after 2 years. Disease management comprised invasive procedures more frequently in men, and during follow-up, men more often needed further revascularization therapy and repeated in-hospital treatment for cardiovascular disease.

## Clinical Presentation

Consistent with data of the literature, women in our pooled analysis were older than men on presentation.[1,3] In contrast to earlier, mostly registry-based data, we did not observe a higher proportion of cardiovascular risk factors in women with suspected ACS or a final diagnosis of ACS. Elevated body mass index, dyslipidemia, smoking and a history of coronary artery disease were more prevalent in men. These results are similar to more recent data of cohorts with patients suggestive of ACS.[24,25]

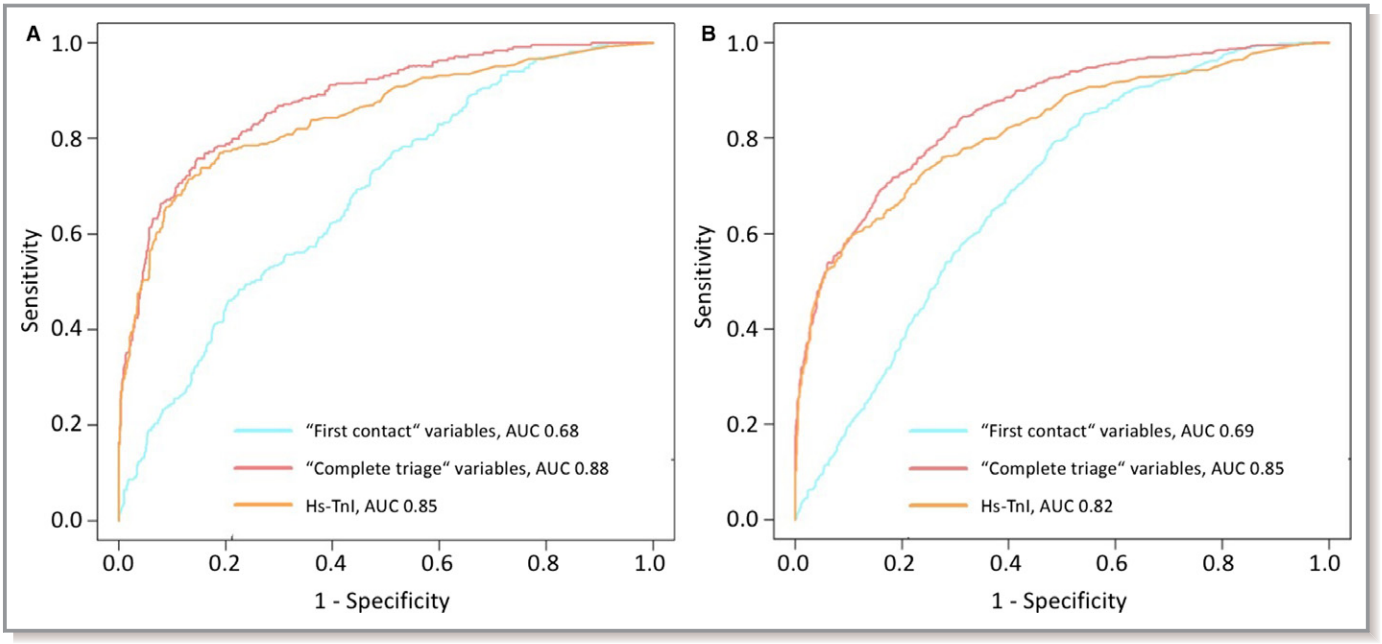


**Figure 1.** ROC curves for LASSO-generated diagnostic models and hs-TnI. Results are shown for women (A) and men (B). The LASSO (logistic regression) was performed on the two different groups of variables considered. We present results for the parameter 1 standard error of the minimum. ROC (receiver operating characteristic) curves and AUC (area under the curve) estimates were corrected for over optimism using bootstrap (with 500 iterations). The ROC curve and AUC for hs-TnI uses the on-admission value.

Previous studies suggested that women with ACS more often present with "atypical" symptoms, in particular with absence of typical chest pain.[3,4,26] In our analyses, the majority of both sexes had some kind of chest pain. In line with prior examinations, other "atypical" symptoms were more often observed in women (dyspnea, nausea and vomiting). It is known that women are more likely to report multiple symptoms in the case of myocardial ischemia.[27] In the overall cohort, women reported more symptoms than men. Thus, atypical symptoms appear to be concurrent to typical presentation with chest pain. In patients with a final diagnosis of ACS, reported symptoms were not significantly different.

A history of coronary artery disease and ST-segment-elevation on the first ECG were significantly associated with sex and ACS. Both variables were more frequent in men, which is consistent with the literature. Women more often present with non-ST-segment elevation myocardial infarction or non-occlusive coronary disease when diagnosed with ACS.[28] However, if present, prior coronary artery disease or ST-segment elevation myocardial infarction were much more strongly associated with ACS in women and may clearly help in the early differential diagnosis.

Furthermore, there was no significant sex-specific difference in time from onset of symptoms to admission at the emergency department in our cohort. Former studies consistently showed longer time from onset of symptoms to presentation to emergency department for women,[29–31] whereas in more recent data, the time delay until hospital admission for women with ACS has diminished and may indicate beneficial trends in ACS management in women.[24]

**Table 4.** Differences in Management of Women and Men

| | | Women (%) | Men (%) | *P* Value |
|---|---|---|---|---|
| Total sample N=2520 | Catheterization No. (%) | 294 (33.4) | 685 (41.8) | <0.001 |
| | Intervention No. (%) | 142 (16.1) | 456 (27.8) | <0.001 |
| | SYNTAX | 4.0 (0, 12.0) | 9.0 (2.0, 18.0) | <0.001 |
| ACS only N=908 | Catheterization No. (%) | 192 (73.8) | 546 (84.3) | <0.001 |
| | Intervention No. (%) | 140 (53.8) | 454 (70.1) | <0.001 |
| | SYNTAX Score | 9.0 (4.0, 15.4) | 12.5 (6.0, 22.0) | <0.001 |

Provided are the number (%) or the median (25th, 75th percentile) score value for the SYNTAX Score. SYNTAX Score information was available in 739 patients of the total sample and in 539 patients with ACS. ACS indicates acute coronary syndrome.

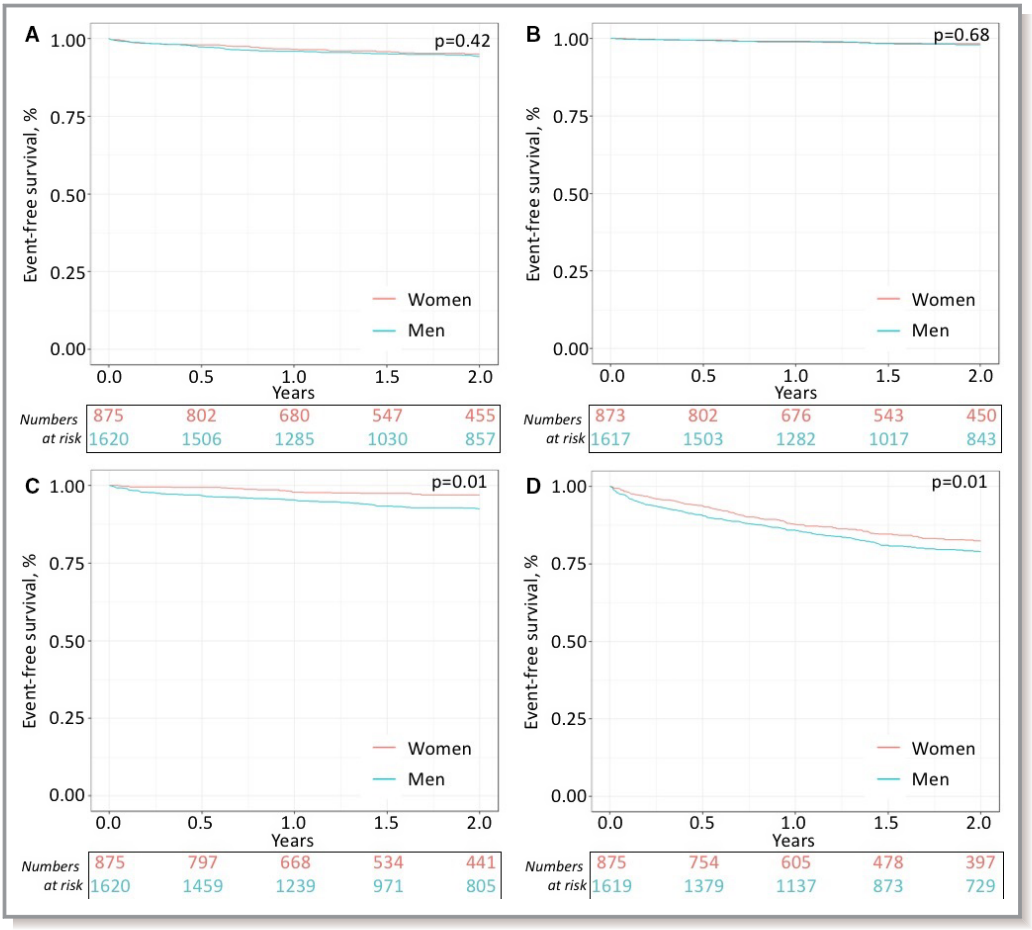


**Figure 2.** Kaplan–Meier curves for event-free survival stratified by sex. Kaplan–Meier curves for the endpoints death (A), myocardial infarction (B), revascularization (C) and cardiovascular rehospitalization (D) are presented. The given *P*-values were calculated using the log-rank test.

The decision to discharge a patient where ACS cannot be excluded may result in a life-threatening outcome, while on the other hand, admission in case of atypical chest pain can lead to unnecessary medical treatment and costs. Risk score models may help the physician in making a timely decision in the emergency setting. Patients with an assumed high probability of an ACS should receive their ECG as fast as possible.

## Diagnostic Accuracy

The diagnosis of ACS is a staged effort.[32] Regardless of whether we considered information available at "first contact" or after "complete triage," diagnostic models performed similarly in women and men. Our findings are supported by recent data published by Hillinger et al which showed high diagnostic accuracy in women at an early stage of clinical assessment in the emergency department, as well as after complete triage.[33]

Although diagnostic accuracy was equal, we observed substantial differences in further work-up of women and men. Women with ACS were less likely to receive coronary angiography or revascularization therapy. This is consistent with the literature[6,34] and could be related to the under-diagnosis of ACS in women recently reported by Shah et al.[35] The topic of sex-specific high-sensitivity troponin cutoffs needs to be addressed in future studies.

## Outcome

Marked differences in clinical characteristics and therapeutic strategies were not related to outcome in our study. Despite older age, differences in risk factor profile, a history of coronary artery disease and distribution of ST-segment elevation myocardial infarction on admission and distinct therapeutic regimens with fewer coronary interventions in women, we could not show significant differences for hard outcomes in our contemporary cohort over 2 years of follow-up. This contradicts former investigations showing higher mortality in women with ACS compared with men, at least at younger ages[3,34] and might support observations indicating the closing of the mortality gap between women and men over the years.[36]

The higher rate of revascularization therapy and cardiac rehospitalization in men might be explained by the higher prevalence of stenotic coronary artery disease as has been demonstrated for multi-vessel disease in men, which may require revascularization therapy more often.[28] This is supported by our results of the SYNTAX Score analyses implicating more severe coronary artery disease in men compared with women with or without ACS.

All including centers had standardized CPUs incorporated in their standard of care. The management of patients suggestive of ACS in these highly specialized facilities proofed to be beneficial.[37] The absence of sex-related differences in hard clinical endpoints may indicate an improved management of both women and men in CPUs, reducing the gender-gap in diagnosis and treatment of ACS.

## Limitations

We cannot exclude a selection bias: inherent in the design of both studies, some individuals with atypical presentation may not have been included in these diagnostic studies. Some less typical symptoms only available in one of the studies were not included in the analysis. There may be slight differences in the adjudication of the final diagnosis because of the use of different, though modern troponin assays: In the stenoCardia study sensitive troponin assays were used, whereas high-sensitivity troponin T was measured in the BACC study. To statistically account for differences of the two cohorts a study indicator was forced into the LASSO calculations. Additionally, logistic regression and LASSO variable selection were performed in both cohorts individually, showing that although the risk of ACS was different in both cohorts, variable selection and odds ratios were comparable. Therefore, we assume the possible distortion of results may not have affected our examination of sex differences significantly.

## Conclusions

Sex-related differences in clinical presentation of patients with suspected ACS did not affect diagnostic accuracy. Although women with ACS were less likely to undergo coronary angiography or revascularization therapy, there were no differences in 2-year mortality or incidence of myocardial infarction. The implementation of CPU algorithms thus appears to diminish sex-related differences in management and outcomes in ACS.

## Author Contributions

Additional Contributions: Susanne Ahrens-Stopperan, Department of General and Interventional Cardiology, University Heart Center Hamburg, University Hospital Hamburg-Eppendorf, served as a study nurse. She did not receive compensation for this role. Nikolas Jarsetz, Jonas Lehmacher, Saskia Gönner, Solveig Kramer, Elena Teltrop, Laura Quantius, Department of General and Interventional Cardiology, University Hospital Hamburg-Eppendorf, helped with patient recruitment and follow-up as part of their doctoral thesis. Data Access and Responsibility: Sörensen and Schnabel had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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## Disclosures

Abbott Diagnostics provided test reagents for high-sensitivity troponin I measurements in both studies. Neumann has received honoraria from Acarix, Blankenberg has received honoraria from Abbott Diagnostics, Siemens, Thermo Fisher, and Roche Diagnostics and is a consultant for Thermo Fisher. None of the other authors declared any conflict of interest related to this study.

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# SUPPLEMENTAL MATERIAL

# Relations of sex to diagnosis and outcomes in acute coronary syndrome

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**Abbreviations**:

ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; hs-TnI, high-sensitivity troponin I; LASSO, least absolute shrinkage and selection operator; NYHA, New York Heart Association; PCI = percutaneous coronary intervention.

**Table S1: Patient characteristics of individuals excluded from analysis.**

| | **Excluded (N=923)** |
|---|---|
| Age (years) | 66.0 (53.0, 75.0) |
| Sex (male) | 615 (66.6) |
| Body mass index (kg/m²) | 26.8 (24.5, 30.0) |
| Systolic Blood pressure (mm Hg) | 144 (130, 160) |
| Heart rate (bpm) | 76.0 (65.8, 88.0) |
| Current smoker (%) | 224 (24.8) |
| Diabetes (%) | 149 (17.4) |
| Dyslipidemia (%) | 477 (51.7) |
| History of coronary artery disease/Bypass/PCI (%) | 349 (39.8) |
| Family history of coronary artery disease (%) | 202 (25.3) |
| Congestive heart failure (%) | 105 (12.7) |
| Atrial fibrillation (%) | 141 (16.0) |
| Stroke (%) | 62 (6.9) |
| Chest pain (%) | 834 (90.5) |
| Radiating chest pain (%) | 367 (40.5) |
| Dyspnea (NYHA III or IV) (%) | 227 (26.3) |
| Nausea or vomiting (%) | 153 (16.9) |
| Diaphoresis (%) | 139 (15.3) |
| Hs-TnI I 0h (ng/L) | 7.0 (3.4, 24.4) |
| eGFR (mL/min for 1.73m²) | 79.6 (61.2, 92.5) |
| All acute coronary syndrome (%) | 314 (34.0) |
| ST-segment elevation myocardial infarction (%) | 62 (6.7) |
| Non-ST-segment elevation myocardial infarction (%) | 137 (14.8) |
| Unstable angina (%) | 115 (12.5) |

eGFR = estimated glomerular filtration rate, hs-TnI = high-sensitivity troponin I, NYHA = New York Heart Association, PCI = percutaneous coronary intervention. For continuous variables quartiles (median (25th percentile, 75th percentile)) are provided, for binary ones number and percent.

**Table S2: Baseline characteristics of patients with the final diagnosis of acute coronary syndrome by sex**

| | Women (N=227) | Men (N=538) | P-value |
|---|---|---|---|
| Age (years) | 70.0 (61.0, 77.0) | 65.0 (55.0, 73.0) | <0.001 |
| Cardiovascular risk factors | | | |
| Body mass index (kg/m²) | 25.5 (22.7, 29.4) | 27.2 (24.9, 30.4) | <0.001 |
| Systolic Blood pressure (mmHg) | 144 (126, 160) | 146 (130, 160) | 0.21 |
| Heart rate (bpm) | 76 (65, 86) | 74 (64, 85) | 0.47 |
| Current smoker (%) | 55 (21.2) | 191 (29.5) | 0.011 |
| Diabetes (%) | 40 (15.4) | 125 (19.3) | 0.18 |
| Dyslipidemia (%) | 167 (64.2) | 459 (70.8) | 0.057 |
| History of coronary artery disease/Bypass/PCI (%) | 109 (41.9) | 299 (46.1) | 0.27 |
| Family history of coronary artery disease (%) | 62 (23.8) | 179 (27.6) | 0.28 |
| Congestive heart failure (%) | 24 (9.2) | 67 (10.3) | 0.71 |
| Atrial fibrillation (%) | 34 (13.1) | 53 (8.2) | 0.033 |
| Stroke (%) | 16 (6.2) | 36 (5.6) | 0.75 |
| Symptoms | | | |
| Chest pain (%) | 228 (87.7) | 602 (92.9) | 0.018 |
| Radiating chest pain (%) | 142 (54.6) | 296 (45.7) | 0.015 |
| Dyspnea (NYHA III or IV) (%) | 142 (54.6) | 296 (45.7) | 0.015 |
| Nausea or vomiting (%) | 68 (26.2) | 101 (15.6) | <0.001 |
| Diaphoresis (%) | 47 (18.1) | 145 (22.4) | 0.18 |
| ≤ 1 Symptom (%) | 143 (55.0) | 364 (56.2) | 0.77 |
| 2-3 Symptoms (%) | 113 (43.5) | 278 (42.9) | 0.88 |
| >3 Symptoms (%) | 4 (1.5) | 6 (0.9) | 0.48 |
| Symptoms onset time < 3h (%) | 84 (33.1) | 227 (35.9) | 0.44 |
| 3h ≥ Symptoms onset time ≤ 6h (%) | 44 (17.3) | 90 (14.2) | 0.25 |
| Symptoms onset time > 6h (%) | 126 (49.6) | 315 (49.8) | 1.00 |
| ECG findings | | | |
| ST-segment depression (%) | 54 (20.8) | 143 (22.1) | 0.72 |
| ST-segment elevation (%) | 62 (23.8) | 205 (31.6) | 0.020 |
| T-wave inversion (%) | 82 (31.5) | 181 (27.9) | 0.29 |
| Left or right bundle branch block (%) | 24 (9.2) | 72 (11.1) | 0.47 |
| Biomarkers | | | |
| Hs-TnI I 0h (ng/L) | 61.0 (11.2, 655.3) | 46.3 (9.9, 417.1) | 0.40 |
| eGFR (mL/min for 1.73m²) | 68 (52, 85) | 80 (65, 94) | <0.001 |
| Final diagnosis | | | |
| ST-segment elevation myocardial infarction (%) | 33 (12.7) | 110 (17.0) | 0.13 |
| Non-ST-segment elevation myocardial infarction (%) | 135 (51.9) | 308 (47.5) | 0.24 |
| Unstable angina (%) | 92 (35.4) | 230 (35.5) | 1.00 |

ECG = electrocardiogram, eGFR = estimated glomerular filtration rate, hs-TnI = high-sensitivity troponin I, NYHA = New York Heart Association, PCI = percutaneous coronary intervention.
The p-values are for Fisher's exact test for categorical variables or the Mann-Whitney test for continuous ones. For continuous variables quartiles (median (25th percentile, 75th percentile)) are provided, for binary ones number and percent.

**Table S3: Baseline characteristics of the BACC cohort**

| | Women (N=415) | Men (N=740) | p-value |
|---|---|---|---|
| Age (years) | 69.0 (54.0, 77.0) | 62.0 (50.0, 73.0) | <0.001 |
| Cardiovascular risk factors | | | |
| Body mass index (kg/m²) | 25.0 (22.3, 28.7) | 26.5 (24.4, 29.6) | <0.001 |
| Systolic Blood pressure (mmHg) | 148 (130, 165) | 145(130, 160) | 0.17 |
| Heart rate (bpm) | 77 (66, 89) | 78 (67, 91) | 0.22 |
| Current smoker (%) | 76 (18.3) | 198 (26.8) | 0.0012 |
| Diabetes (%) | 48 (11.6) | 113 (15.3) | 0.092 |
| Dyslipidemia(%) | 150 (36.1) | 329 (44.5) | 0.0062 |
| History of coronary artery disease/Bypass/PCI (%) | 108 (26.0) | 285 (38.5) | <0.001 |
| Family history of coronary artery disease (%) | 73 (17.6) | 139 (18.8) | 0.64 |
| Congestive heart failure (%) | 48 (11.6) | 114 (15.4) | 0.077 |
| Atrial fibrillation (%) | 78 (18.8) | 122 (16.5) | 0.33 |
| Stroke (%) | 30 (7.2) | 46 (6.2) | 0.54 |
| Symptoms | | | |
| Chest pain (%) | 327 (78.8) | 610 (82.4) | 0.14 |
| Radiating chest pain (%) | 132 (31.8) | 202 (27.3) | 0.12 |
| Dyspnea (NYHA III or IV) (%) | 98 (23.6) | 136 (18.4) | 0.039 |
| Nausea or vomiting (%) | 20 (4.8) | 78 (10.5) | <0.001 |
| Diaphoresis (%) | 58 (14.0) | 107 (14.5) | 0.86 |
| Syncope (%) | 16 (3.9) | 34 (4.6) | 0.65 |
| Abdominal pain (%) | 30 (7.2) | 35 (4.7) | 0.084 |
| ≤ 1 Symptom (%) | 305 (73.5) | 552 (74.6) | 0.73 |
| 2-3 Symptoms (%) | 108 (26.0) | 187 (25.3) | 0.78 |
| >3 Symptoms (%) | 2 (0.5) | 1 (0.1) | 0.29 |
| Symptoms onset time < 3h (%) | 108 (27.8) | 213 (30.9) | 0.33 |
| 3h ≥ Symptoms onset time ≤ 6h (%) | 55 (14.2) | 74 (10.7) | 0.097 |
| Symptoms onset time > 6h (%) | 225 (58.0) | 403 (58.4) | 0.90 |
| ECG findings | | | |
| ST-segment depression (%) | 43 (10.4) | 53 (7.2) | 0.075 |
| ST-segment elevation (%) | 16 (3.9) | 47 (6.4) | 0.080 |
| T-wave-inversion (%) | 47 (11.3) | 79 (10.7) | 0.77 |
| Left or right bundle branch block (%) | 28 (6.7) | 64 (8.6) | 0.31 |
| Biomarkers | | | |
| Hs-TnI 0h (ng/L) | 6.7 (2.8, 23.7) | 7.6 (3.4, 23.2) | 0.14 |
| eGFR (mL/min for 1.73m²) | 72 (53, 91) | 79 (61, 94) | 0.0011 |
| Final diagnosis | | | |
| All acute coronary syndrome (%) | 132 (31.8) | 297 (40.1) | 0.0052 |
| ST-segment elevation myocardial infarction (%) | 11 (2.7) | 38 (5.1) | 0.048 |
| Non-ST-segment elevation myocardial infarction (%) | 84 (20.2) | 147 (19.9) | 0.88 |
| Unstable angina pectoris (%) | 37 (8.9) | 112 (15.1) | 0.0025 |

ECG = electrocardiogram, eGFR = estimated glomerular filtration rate, hs-TnI = high-sensitivity troponin I, NYHA = New York Heart Association, PCI = percutaneous coronary intervention.

The p-values are for Fisher's exact test for categorical variables or the Mann-Whitney test for continuous ones for continuous variables quartiles (median (25th percentile, 75th percentile)) are provided, for binary ones number and percent.

**Table S4: Baseline characteristics of included patients from the stenoCardia cohort**

| | Women (N=415) | Men (N=808) | p-value |
|---|---|---|---|
| Age (years) | 66.0 (55.0, 74.0) | 61.0 (50.0, 70.0) | <0.001 |
| Cardiovascular risk factors | | | |
| Body mass index (kg/m²) | 26.7 (23.9, 30.1) | 27.3 (25.0, 30.4) | 0.0021 |
| Systolic Blood pressure (mmHg) | 140 (129, 160) | 140 (125, 155) | 0.16 |
| Heart rate (bpm) | 72 (63, 80) | 70 (62, 80) | 0.52 |
| Current smoker (%) | 81 (19.5) | 210 (26.0) | 0.013 |
| Diabetes (%) | 52 (12.5) | 113 (14.0) | 0.54 |
| Dyslipidemia (%) | 305 (73.5) | 594 (73.5) | 1.00 |
| History of coronary artery disease/Bypass/PCI (%) | 102 (24.6) | 288 (35.6) | <0.001 |
| Family history of coronary artery disease (%) | 133 (32.0) | 250 (30.9) | 0.70 |
| Congestive heart failure (%) | 12 (2.9) | 29 (3.6) | 0.62 |
| Atrial fibrillation (%) | 37 (8.9) | 57 (7.1) | 0.26 |
| Stroke (%) | 20 (4.8) | 36 (4.5) | 0.77 |
| Symptoms | | | |
| Chest pain (%) | 407 (98.1) | 791 (97.9) | 1.00 |
| Radiating chest pain (%) | 249 (60.0) | 394 (48.8) | <0.001 |
| Dyspnea (NYHA III or IV) (%) | 85 (20.5) | 150 (18.6) | 0.44 |
| Nausea or vomiting (%) | 153 (36.9) | 167 (20.7) | <0.001 |
| Diaphoresis (%) | 98 (23.6) | 195 (24.1) | 0.89 |
| Burning sensation No. (%) | 27 (6.5) | 66 (8.2) | 0.36 |
| Heaviness No. (%) | 15 (3.6) | 30 (3.7) | 1.00 |
| Panic, anxiety No. (%) | 128 (30.8) | 238 (29.5) | 0.64 |
| Edema No. (%) | 11 (2.7) | 27 (3.3) | 0.60 |
| Fatigue No. (%) | 40 (9.6) | 82 (10.1) | 0.84 |
| ≤ 1 Symptom (%) | 171 (41.2) | 421 (52.1) | <0.001 |
| 2-3 Symptoms (%) | 241 (58.1) | 380 (47.0) | <0.001 |
| >3 Symptoms (%) | 3 (0.7) | 7 (0.9) | 1.00 |
| Symptoms onset time < 3h (%) | 161 (38.8) | 319 (39.5) | 0.85 |
| 3h ≥ Symptoms onset time ≤ 6h (%) | 84 (20.2) | 161 (19.9) | 0.94 |
| Symptoms onset time > 6h (%) | 170 (41.0) | 328 (40.6) | 0.90 |
| ECG findings | | | |
| ST-segment depression (%) | 53 (12.8) | 152 (18.8) | 0.0076 |
| ST-segment elevation (%) | 100 (24.1) | 339 (42.0) | <0.001 |
| T-wave-inversion (%) | 124 (29.9) | 259 (32.1) | 0.47 |
| Left or right bundle branch block (%) | 36 (8.7) | 101 (12.5) | 0.045 |
| Biomarkers | | | |
| Hs-TnI 0h (ng/L) | 5.4 (2.7, 22.2) | 9.1 (4.1, 50.3) | <0.001 |
| eGFR (mL/min for 1.73m²) | 78 (64, 91) | 86 (74, 98) | <0.001 |
| Final diagnosis | | | |
| All acute coronary syndrome (%) | 116 (28.0) | 312 (38.6) | <0.001 |
| ST-segment elevation myocardial infarction (%) | 21 (5.1) | 65 (8.0) | 0.059 |
| Non-ST-segment elevation myocardial infarction (%) | 48 (11.6) | 144 (17.8) | 0.0047 |
| Unstable angina pectoris (%) | 47 (11.3) | 103 (12.7) | 0.52 |

ECG = electrocardiogram, eGFR = estimated glomerular filtration rate, hs-TnI = high-sensitivity troponin I, NYHA = New York Heart Association, PCI = percutaneous coronary intervention.
The p-values are for Fisher's exact test for categorical variables or the Mann-Whitney test for continuous ones. For continuous variables the quartiles are given, for binary ones frequencies. The quartiles are given on the following format: Median (25th percentile, 75th percentile).

**Table S5: Logistic regression models for prediction of ACS including interaction with sex in the BACC cohort**

| Predictor of interest | Sex interaction p-value | Category | OR (95% CI) | p-value |
|---|---|---|---|---|
| Age | 0.59 | Women | 1.03 (1.01, 1.04) | <0.001 |
| | | Men | 1.03 (1.02, 1.05) | <0.001 |
| Body mass index | 0.22 | Women | 0.99 (0.95, 1.03) | 0.61 |
| | | Men | 1.02 (0.99, 1.05) | 0.19 |
| Systolic blood pressure | 0.038 | Women | 1.00 (0.99, 1.00) | 0.25 |
| | | Men | 1.01 (1.00, 1.01) | 0.057 |
| Heart rate (log) | 0.44 | Women | 1.36 (0.57, 3.20) | 0.48 |
| | | Men | 0.89 (0.47, 1.68) | 0.71 |
| Current smoker | 0.058 | Women | 0.72 (0.41, 1.25) | 0.26 |
| | | Men | 1.34 (0.97, 1.86) | 0.08 |
| Diabetes | 0.96 | Women | 1.47 (0.78, 2.72) | 0.22 |
| | | Men | 1.50 (1.00, 2.25) | 0.047 |
| Dyslipidemia | 0.72 | Women | 2.86 (1.87, 4.41) | <0.001 |
| | | Men | 3.16 (2.33, 4.30) | <0.001 |
| History of coronary artery disease /bypass/PCI | 0.17 | Women | 4.56 (2.88, 7.31) | <0.001 |
| | | Men | 3.10 (2.28, 4.23) | <0.001 |
| Family history of coronary artery disease | 0.079 | Women | 0.91 (0.52, 1.56) | 0.74 |
| | | Men | 1.64 (1.13, 2.37) | 0.0091 |
| Congestive heart failure | 0.91 | Women | 1.47 (0.78, 2.72) | 0.22 |
| | | Men | 1.41 (0.94, 2.11) | 0.091 |
| Atrial fibrillation | 0.089 | Women | 0.94 (0.55, 1.59) | 0.83 |
| | | Men | 0.52 (0.34, 0.79) | 0.0026 |
| Stroke | 0.45 | Women | 0.77 (0.31, 1.70) | 0.53 |
| | | Men | 0.50 (0.25, 0.97) | 0.047 |
| Dyspnea (NYHA III or IV) | 0.54 | Women | 2.00 (1.25, 3.20) | 0.0036 |
| | | Men | 1.66 (1.14, 2.42) | 0.0076 |
| Chest pain | 0.088 | Women | 0.94 (0.57, 1.56) | 0.79 |
| | | Men | 1.64 (1.10, 2.49) | 0.016 |
| Radiating chest pain | 0.41 | Women | 1.82 (1.18, 2.81) | 0.0069 |
| | | Men | 1.45 (1.05, 2.01) | 0.025 |
| Nausea and vomiting | 0.72 | Women | 0.99 (0.53, 1.78) | 0.97 |
| | | Men | 0.85 (0.48, 1.46) | 0.56 |
| Diaphoresis | 0.26 | Women | 2.24 (0.90, 5.59) | 0.08 |
| | | Men | 1.24 (0.77, 1.98) | 0.38 |
| ST-segment depression | 0.49 | Women | 2.77 (1.46, 5.30) | 0.0018 |
| | | Men | 3.78 (2.10, 7.12) | <0.001 |
| ST-segment elevation | 0.12 | Women | 36.15 (7.20, 657.53) | <0.001 |
| | | Men | 8.19 (3.97, 19.13) | <0.001 |
| T-wave-inversion | 0.73 | Women | 1.87 (1.00, 3.46) | 0.047 |
| | | Men | 2.14 (1.34, 3.45) | 0.0016 |
| Left or right bundle branch block | 0.76 | Women | 1.67 (0.75, 3.62) | 0.2 |
| | | Men | 1.44 (0.86, 2.41) | 0.16 |
| Log(hs-TnI) | 0.006 | Women | 2.77 (2.27, 3.48) | <0.001 |
| | | Men | 1.99 (1.76, 2.27) | <0.001 |
| eGFR | 0.22 | Women | 0.98 (0.97, 0.99) | <0.001 |
| | | Men | 0.99 (0.98, 0.99) | <0.001 |

eGFR = estimated glomerular filtration rate, hs-TnI = high-sensitivity troponin I, NYHA = New York Heart Association, PCI = percutaneous coronary intervention. Logistic regression models for ACS

status include the predictor of interest x sex interaction. For each independent variable, a separate model was computed.

**Table S6: Logistic regression models for prediction of ACS including interaction with sex in the stenoCardia cohort**

| Predictor of interest | Sex interaction p-value | Category | OR (95% CI) | p-value |
|---|---|---|---|---|
| Age | 0.87 | Women | 1.03 (1.02, 1.05) | <0.001 |
| | | Men | 1.03 (1.02, 1.05) | <0.001 |
| Body mass index | 0.13 | Women | 0.98 (0.94, 1.02) | 0.31 |
| | | Men | 1.02 (0.99, 1.05) | 0.27 |
| Systolic blood pressure | 0.067 | Women | 1.00 (0.99, 1.01) | 0.55 |
| | | Men | 1.01 (1.00, 1.01) | 0.018 |
| Heart rate (log) | 0.77 | Women | 1.60 (0.53, 4.82) | 0.41 |
| | | Men | 1.32 (0.68, 2.57) | 0.42 |
| Current smoker | 0.14 | Women | 1.85 (1.14, 2.98) | 0.012 |
| | | Men | 1.20 (0.88, 1.62) | 0.24 |
| Diabetes | 0.96 | Women | 1.59 (0.88, 2.82) | 0.12 |
| | | Men | 2.39 (1.63, 3.53) | <0.001 |
| Dyslipidemia | 0.25 | Women | 1.16 (0.73, 1.87) | 0.54 |
| | | Men | 1.60 (1.17, 2.21) | 0.0035 |
| History of coronary artery disease /bypass/PCI | 0.037 | Women | 2.25 (1.44, 3.52) | <0.001 |
| | | Men | 1.29 (0.97, 1.70) | 0.076 |
| Family history of coronary artery disease | 0.77 | Women | 0.82 (0.53, 1.26) | 0.38 |
| | | Men | 0.89 (0.67, 1.18) | 0.43 |
| Congestive heart failure | 0.58 | Women | 1.48 (0.45, 4.38) | 0.49 |
| | | Men | 1.02 (0.49, 2.06) | 0.96 |
| Atrial fibrillation | 0.58 | Women | 0.84 (0.38, 1.70) | 0.64 |
| | | Men | 0.64 (0.36, 1.10) | 0.12 |
| Stroke | 0.60 | Women | 1.54 (0.60, 3.69) | 0.34 |
| | | Men | 2.05 (1.11, 3.85) | 0.022 |
| Dyspnea (NYHA III or IV) | 0.17 | Women | 0.89 (0.53, 1.47) | 0.66 |
| | | Men | 1.37 (0.97, 1.92) | 0.073 |
| Chest pain | 0.78 | Women | 1.01 (0.29, 4.68) | 0.98 |
| | | Men | 1.28 (0.49, 3.71) | 0.62 |
| Radiating chest pain | 0.93 | Women | 1.70 (1.11, 2.64) | 0.016 |
| | | Men | 1.66 (1.27, 2.18) | <0.001 |
| Nausea and vomiting | 0.85 | Women | 1.14 (0.75, 1.74) | 0.53 |
| | | Men | 1.09 (0.79, 1.50) | 0.61 |
| Diaphoresis | 0.18 | Women | 1.33 (0.83, 2.09) | 0.22 |
| | | Men | 1.94 (1.42, 2.64) | <0.001 |
| ST-segment depression | 0.63 | Women | 3.67 (2.09, 6.49) | <0.001 |
| | | Men | 3.13 (2.22, 4.42) | <0.001 |
| ST-segment elevation | 0.0039 | Women | 2.52 (1.60, 3.97) | <0.001 |
| | | Men | 1.45 (1.10, 1.90) | 0.0078 |
| T-wave-inversion | 0.018 | Women | 3.18 (2.07, 4.91) | <0.001 |
| | | Men | 1.71 (1.28, 2.27) | <0.001 |
| Left or right bundle branch block | 0.52 | Women | 1.24 (0.59, 2.48) | 0.56 |
| | | Men | 0.94 (0.62, 1.41) | 0.76 |
| Log(hs-TnI) | 0.050 | Women | 2.04 (1.78, 2.37) | <0.001 |
| | | Men | 2.48 (2.19, 2.83) | <0.001 |
| eGFR | 0.22 | Women | 0.98 (0.97, 0.99) | <0.001 |
| | | Men | 0.99 (0.98, 0.99) | <0.001 |

eGFR = estimated glomerular filtration rate, hs-TnI = high-sensitivity troponin I, NYHA = New York Heart Association, PCI = percutaneous coronary intervention. Logistic regression models for ACS

status include the predictor of interest x sex interaction. For each independent variable, a separate model was computed.

**Table S7: Odds ratios for variables selected by LASSO regression for the diagnosis of ACS in the BACC-cohort**

| | "First Contact" Odds ratio | "Complete Triage" Odds ratio |
|---|---|---|
| Age | 1.02 | 1.00 |
| Cardiovascular risk factors | | |
| Body mass index | | |
| Systolic blood pressure | | |
| Heart rate | | |
| Current smoker | 1.12 | |
| Diabetes | | |
| Dyslipidemia | 1.63 | 1.62 |
| History of coronary artery disease /Bypass/PCI | 1.90 | 2.44 |
| Family history of coronary artery disease | 1.15 | 1.13 |
| Congestive heart failure | | 0.87 |
| Atrial fibrillation | 0.67 | 0.64 |
| Stroke | 0.76 | 0.89 |
| Symptoms | | |
| Chest pain | | 1.10 |
| Radiating chest pain | 1.29 | 1.14 |
| Dyspnea (NYHA III or IV) | 1.14 | |
| Nausea or vomiting | | |
| Diaphoresis | 1.12 | 1.18 |
| ECG findings | | |
| ST-segment depression | not included | 1.75 |
| ST-segment elevation | not included | 4.53 |
| T-wave-inversion | not included | |
| Left or right bundle branch block | not included | |
| Biomarkers | | |
| Hs-TnI 0h | not included | 1.88 |
| eGFR | not included | |

ECG = electrocardiogram, eGFR = estimated glomerular filtration rate, hs-TnI = high-sensitivity troponin I, NYHA = New York Heart Association PCI = percutaneous coronary intervention. Hs-TnI and heart rate were log-transformed. The LASSO penalization parameter lambda was chosen by optimization of the mean deviance in 10-fold cross-validation. Shown are the results for the parameter 1 standard error of the minimum.

**Table S8: Odds ratios for variables selected by LASSO regression for the diagnosis of ACS in the stenoCardia-cohort**

| | "First Contact" Odds ratio | "Complete Triage" Odds ratio |
|---|---|---|
| Age | 1.03 | 1.00 |
| Cardiovascular risk factors | | |
| Body mass index | | |
| Systolic blood pressure | | |
| Heart rate | | |
| Current smoker | 1.53 | |
| Diabetes | 1.42 | 1.35 |
| Dyslipidemia | | |
| History of coronary artery disease /Bypass/PCI | | 1.16 |
| Family history of coronary artery disease | | |
| Congestive heart failure | | 0.87 |
| Atrial fibrillation | 0.63 | |
| Stroke | 0.763 | 0.89 |
| Symptoms | | |
| Chest pain | | |
| Radiating chest pain | 1.43 | 1.17 |
| Dyspnea (NYHA III or IV) | | |
| Nausea or vomiting | | |
| Diaphoresis | 1.28 | 1.17 |
| ECG findings | | |
| ST-segment depression | not included | 1.15 |
| ST-segment elevation | not included | |
| T-wave-inversion | not included | |
| Left or right bundle branch block | not included | 0.93 |
| Biomarkers | | |
| Hs-TnI 0h | not included | 1.94 |
| eGFR | not included | |

ECG = electrocardiogram, eGFR = estimated glomerular filtration rate, hs-TnI = high-sensitivity troponin I, NYHA = New York Heart Association PCI = percutaneous coronary intervention. Hs-TnI and heart rate were log-transformed. The LASSO penalization parameter lambda was chosen by optimization of the mean deviance in 10-fold cross-validation. Shown are the results for the parameter 1 standard error of the minimum.

**Data S1 - Detailed information about the LASSO method**

The least absolute shrinkage and selection operator (LASSO)[1] shrinks the coefficients toward zero by imposing a penalty on their size. Some of the estimated coefficients may be exactly zero, so the LASSO also performs variable selection. Shrinking the coefficients may reduce the variance of the predictions, increasing prediction accuracy, at the price of introducing some bias.

More precisely, let $\beta = (\beta_0, \beta_1, \dots, \beta_p)^T$ be a vector of regression coefficients from a logistic regression model, where $\beta_0$ is the intercept, and $l(\beta)$ is the binomial log-likelihood function. The coefficients $\beta$ in logistic regression are usually estimated by maximizing $l(\beta)$ (maximum likelihood estimation). The LASSO on the other hand introduces a constraint on the size of the coefficients, which are estimated by maximizing for a fixed $\lambda > 0$, the quantity $(\beta) - \lambda \sum_{j=1}^{p} |\beta_j|$. The penalization parameter $\lambda$ is a tuning parameter and it is often chosen using cross-validation. The larger $\lambda$ is, the more shrinkage will be applied to the coefficients.

For the current analyses we used the LASSO as implemented in the R package glmnet.[2] To choose the penalization parameter the mean deviance was minimized in 10-fold cross-validation. To achieve a more parsimonious model, that the one that would be obtained using the $\lambda$ where the optimum was achieved, the largest $\lambda$ within 1 standard error of the former $\lambda$ (optimum) was chosen.

Methods that perform shrinkage, like the LASSO, have been shown in simulation studies to perform better than the popularstepwise regression.[3,4] The latter tends to produce overfitted models, whereas using shrinkage may avoid this problem (for a detailed list of problems with stepwise regression see chapter 4 in Harrell[5]).

**Literature**


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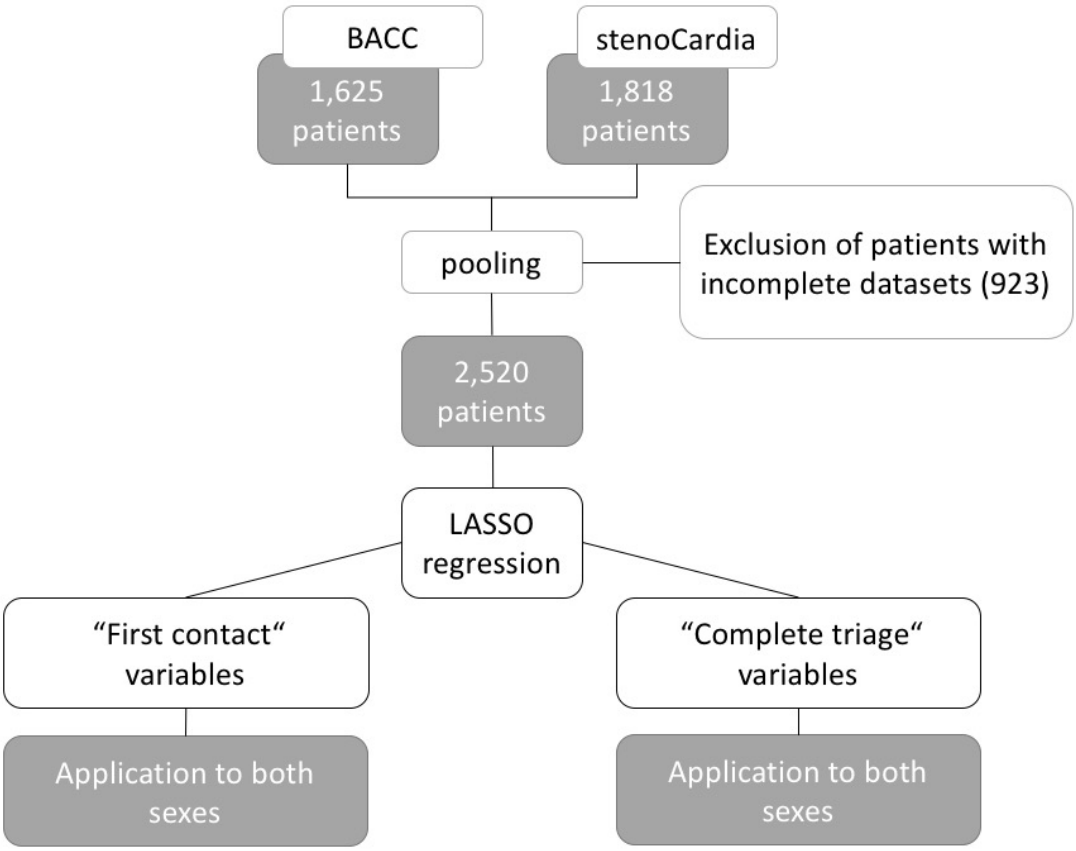
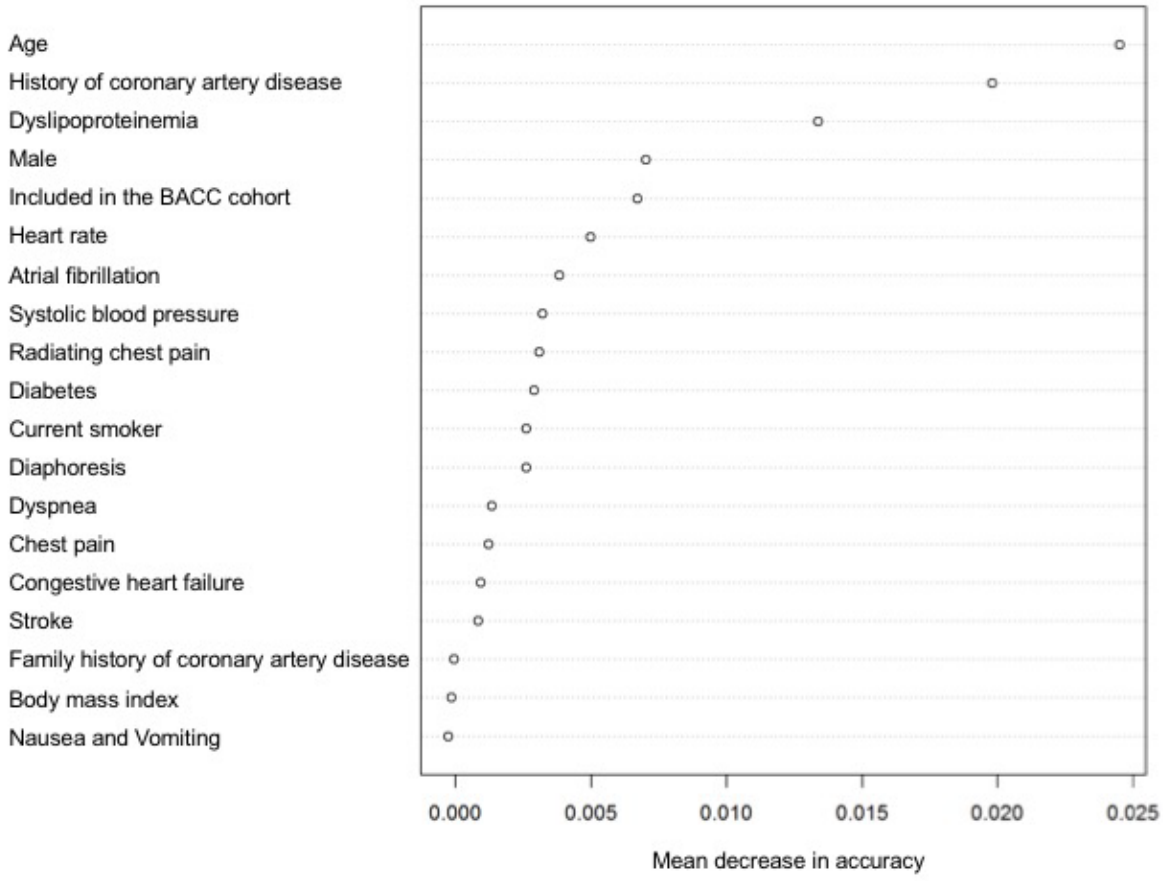
**Figure S1: Flowchart of LASSO-generated diagnostic models**



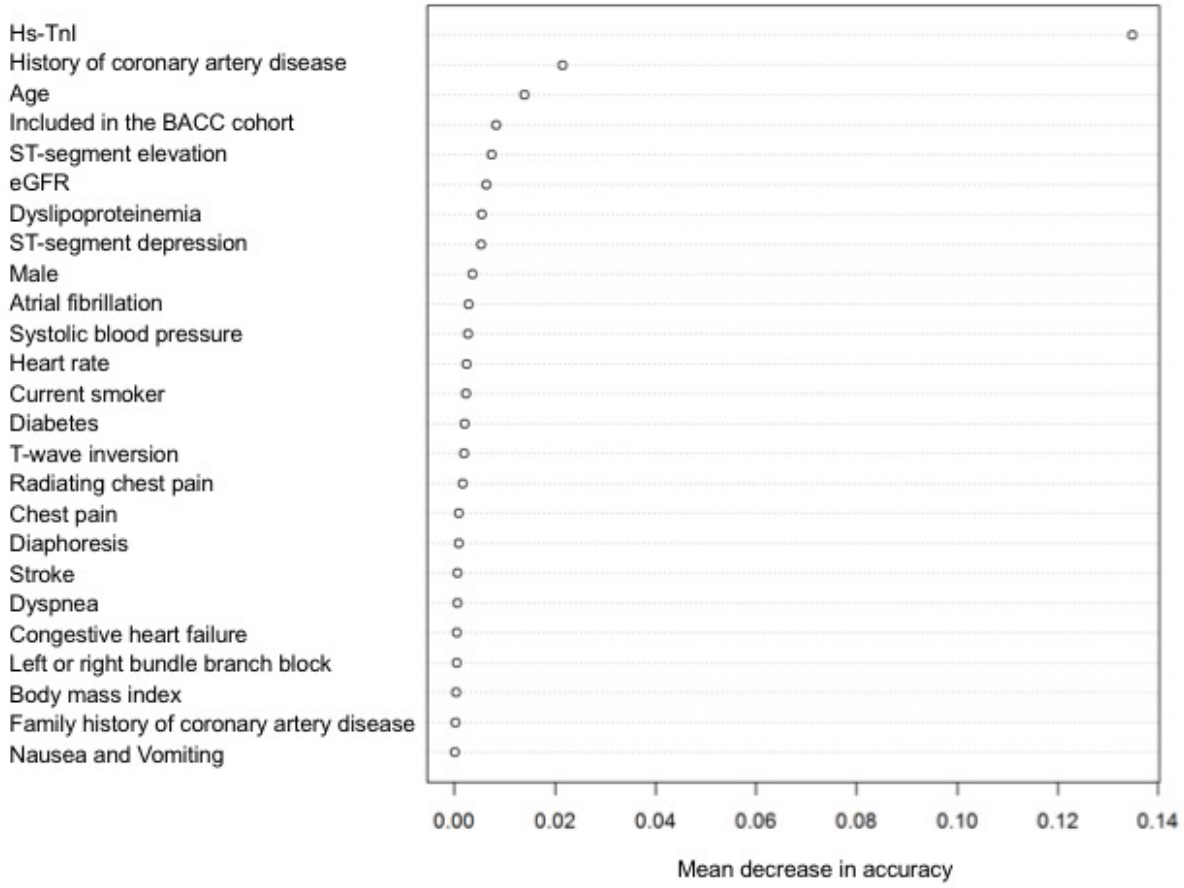

LASSO = least absolute shrinkage and selection operator

**Figure S2: Variable importance according to random forest for first contact variables**



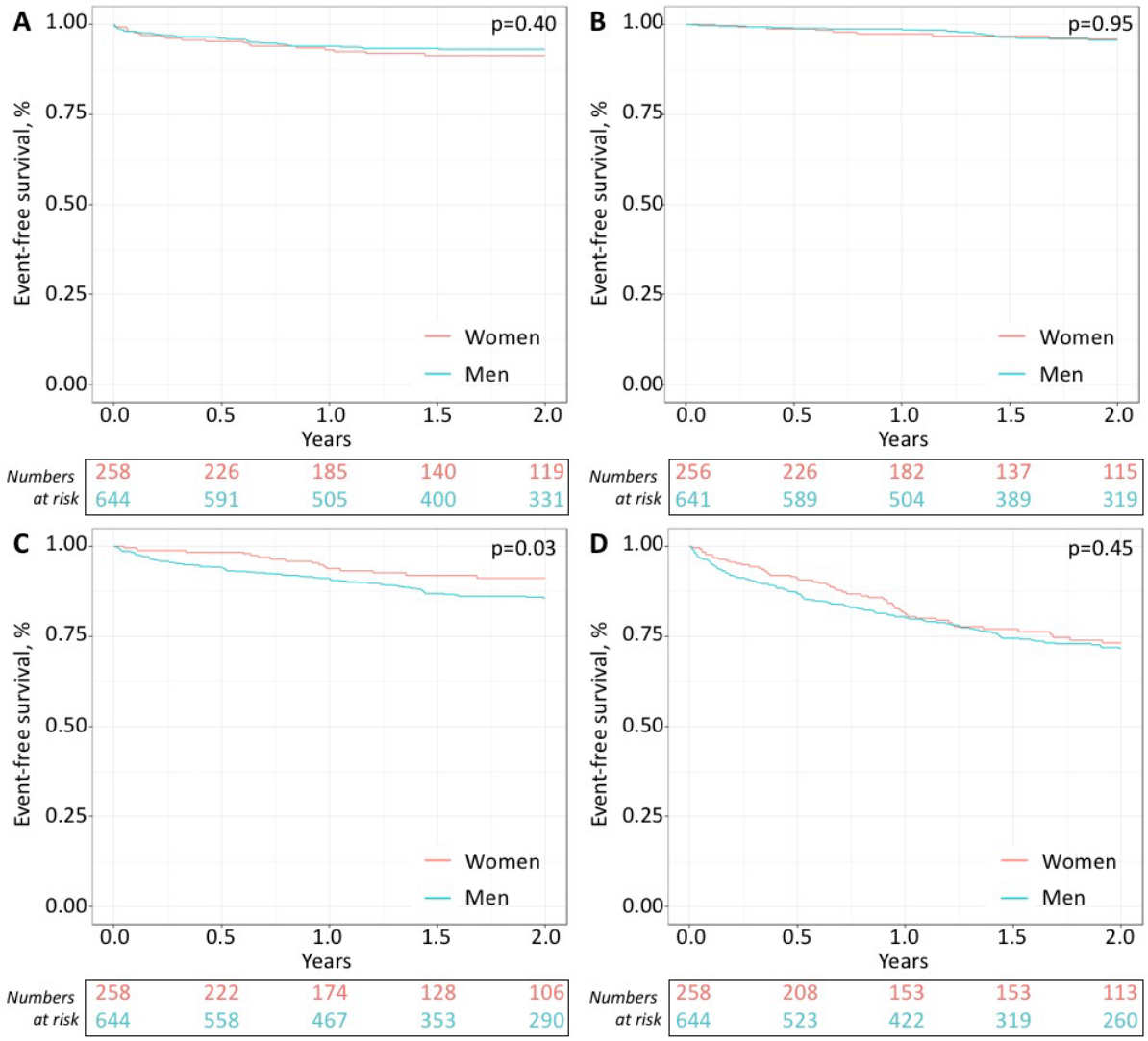

Variable importance according to random forest using “first contact” variables.

**Figure S3: Variable importance according to random forest for all variables after complete triage**




Variable importance according to random forest using “complete triage” variables.

**Figure S4: Kaplan-Meier curves for event-free survival stratified by sex for patients with a final diagnosis of acute coronary syndrome**




Kaplan-Meier curves for the endpoints death (A), myocardial infarction (B), revascularization (C) and cardiac rehospitalization are presented. The p-values were calculated using the log-rank test.